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Ozonolysis of Morita–Baylis–Hillman adducts originated from aromatic aldehydes: an expeditious diastereoselective approach for the preparation of α,β-dihydroxy-esters☆

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Abstract—We disclose herein ozonolysis of Morita–Baylis–Hillman adducts originated from aromatic aldehydes. This efficient reaction provides α-ketoesters with different substitution patterns on the aromatic ring. Diastereoselective reduction of the corresponding α-ketoester obtained in the oxidative cleavage step provides α,β-dihydroxy-esters with excellent degree of *anti* diastereoselection. The method is simple and easy to execute and is therefore a valuable alternative to prepare either α-ketoesters or α,β-dihydroxy-esters.

In the last years, the Morita–Baylis–Hillman reaction (MBH) has attracted much attention as a simple and straightforward alternative to form a new C–C σ bond.[1,2] The resulted MBH adducts have found vast application as a versatile building block to generate either bioactive compounds[3] or useful synthetic intermediates.[4] The synthetic versatility of these adducts comes from the three functionalities present in the same molecular backbone, disposed in a unique fashion.

We have been involved in a research program aimed at the synthesis of isoquinolinones from MBH adducts.[5] Our interest was focused on preparing β-ketoesters from these adducts (**3** or **4**) and their use as starting material for the synthesis of functionalized isoquinolinones (Fig. 1).

The simplest way to prepare the required α-ketoesters from MBH adducts was via ozonolysis. Unfortunately, however, the oxidation reaction failed to work as required and we were able to isolate products resulting from the complete degradation of the aromatic ring.[6] These results forced us to abandon this approach.[7]

But Doutheau and co-workers.[8] described in 2005 a successful oxidative cleavage of the double bond of some MBH adducts originated from aliphatic aldehydes. One of the ozonolyzed adducts was used as starting material for the preparation of (*S*)-4,5-dihydroxy-2,3-pentadione (DPD).

This impressive achievement stimulated us to revisit the ozonolysis reaction of MBH adducts originated from aromatic aldehydes. We are interested in this particular oxidative cleavage mainly for two reasons. First, this strategy seems to us to be a very efficient way to access highly functionalized α-ketoesters, which could be used as starting materials for the synthesis of diols, α-amino-esters, or even tricarbonyl compounds.[9] Secondly, the double bond oxidation of MBH adducts originated from aromatic aldehydes is troublesome and requires special attention to avoid the extensive degradation already observed by us and others.[6] The success on the ozonolysis of MBH adducts could also contribute to extend the scope of this interesting reaction described by Doutheau.

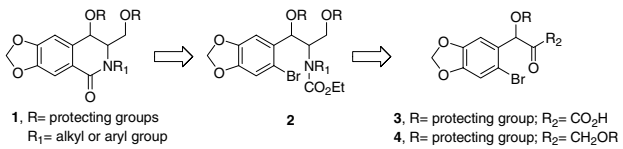

Figure 1. Isoquinolinones from α-keto esters or keto alcohols.

☆ In memoriam of Professor Helena Ferraz for the outstanding contributions she gave to the Brazilian Chemical Community.

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In this Letter, we describe a successful ozonolysis reaction of several MBH adducts prepared from aromatic aldehydes. We also exemplified the synthetic versatility of α-ketoesters by their diastereoselective transformation into α,β-dihydroxy-esters.

The MBH adducts were prepared according to a methodology we described some years ago.[10a,b] Assuming an eventual chemical instability of the α-keto-β-hydroxy esters obtained in the oxidative step, we decided to protect the secondary hydroxyl group of all MBH adducts using TBS or acetate as protecting groups. The results concerning the reaction of MBH as well as those referring to the protective step are summarized in Table 1.

Having all protected Morita–Baylis–Hillman adducts in hand, we submitted them to ozonolysis. Basically, the ozonolysis reactions were performed using two different solvents (methanol and dichloromethane) at −78 °C. For both solvents, the oxidation works properly and provides the α-keto-β-hydroxy esters in moderate to good yields after a few minutes (15–20 min). This reaction is very time sensitive. If it is run overtime, extensive degradation occurs and only the product of overoxidation is isolated. The reaction should be followed carefully, by TLC for instance, and after a few minutes only the ozonolyzed product is observed (a more polar spot is detected).

The ozonolysis works efficiently with most MBH adducts leading to different α-keto-β-hydroxy esters with a variety of substituents on the aromatic ring. Even for those examples having either no substituent, or electron-donating substituents on aromatic ring (Table 2, entries 1, 2 and 3) the reaction works efficiently, without any trace of oxidative degradation of the aromatic ring.[12] In the particular case of piperonal (Table 2, entry 2), the reaction is stopped as soon as the sign of decomposition was detected by TLC (ca 7 min) with recovery and recycling of the starting material. If this reaction, for this particular adduct, is run to the point that all starting material is consumed, only 10% product yield is obtained. The oxidation of acetylated derivative (**18**) works equally well, with the same experimental behavior observed for the silylated derivatives. Table 2 summarizes all results, and all spectroscopic data are compatible with the structure of the α-ketoester compounds.[11]

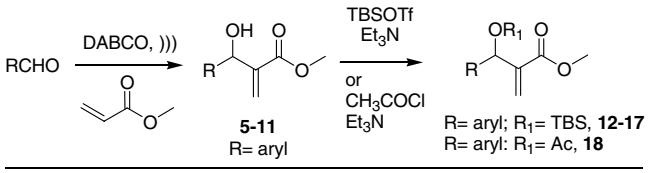
Trying to simplify the method we decided to test the ozonolysis reaction directly over the unprotected MBH adducts.

To our delight therefore, the reaction works efficiently for all cases tested, and we were also able to obtain the desired α-ketoesters in moderate to good yields after just a few minutes (Table 2, entries 8–12). Even for MBH adducts having electron rich aromatic rings, the reaction works with just a low level of overoxidation.

In this stage of the work we have developed a simple and direct approach to prepare α-ketoesters having an aromatic ring with different substituent patterns. The method is fast and is a valuable alternative to prepare this type of α-ketoesters.[12] To demonstrate its synthetic versatility we have performed some chemical transformations on these synthetic versatile compounds.

A wide range of important compounds in organic chemistry comprise the 1,2-diol unit.[13] This motif

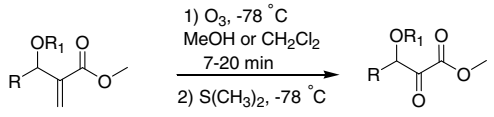
Table 1. Preparation of the protected MBH adducts



Entry	Aldehyde	MBH[a,b,c] (%)	Protected adduct[b,c] (%)
1	Benzaldehyde	**5** (70)	**12** (92)
2	Piperonal	**6** (73)	**13** (96)
3	Anisaldehyde	**7** (80)	**14** (98)
4	3,5-F,F-Benzaldehyde	**8** (80)	**15** (77)
5	6-Br-Piperonal	**9** (85)	**16** (95)
6	4-NO_2-Benzaldehyde	**10** (99)	**17** (97)
7	4-CH_3SO_2-Benzaldehyde	**11** (93)	**18** (80)

[a] The Morita–Baylis–Hillman reactions were performed using methyl acrylate as solvent in an ultrasound bath (1000 W, 40 Hz).
[b] The yield refers to isolated and purified product.
[c] All spectral data are compatible for each compound, according to data available in the literature.

Table 2. Ozonolysis of the protected and unprotected MBH adducts



R= aryl; R_1= TBS,**12-17**
R= aryl: R_1= Ac, **18**
R= aryl; R_1= H (**5**, **7**, **9**, **10**, **26**)

R= aryl; R_1= TBS, **19-24**
R= aryl: R_1= Ac, **25**
R= aryl; R_1= H (**27-31**)

Entry	Protected MBH adducts	α-Ketoesters[a,b,c] (%)
1	**12**, R = phenyl	**19** (67)
2	**13**, R = piperonyl	**20** (68)
3	**14**, R = 4-OCH_3-phenyl	**21** (79)
4	**15**, R = 3,5-difluorophenyl	**22** (77)
5	**16**, R = 6-Br-piperonyl	**23** (85)
6	**17**, R = 4-NO_2-phenyl	**24** (82)
7	**18**, R = 4-CH_3SO_2-phenyl	**25** (71)
	Unprotected MBH adducts	
8	**5**, R = phenyl	**26** (75)[d]
9	**7**, R = 4-OCH_3-phenyl	**27** (85)[d]
10	**9**, R = 6-Br-piperonyl	**28** (82)[d]
11	**10**, R = 4-NO_2-phenyl	**29** (70)[d]
12	**26**, R = 3-Cl-phenyl	**30** (83)[d]

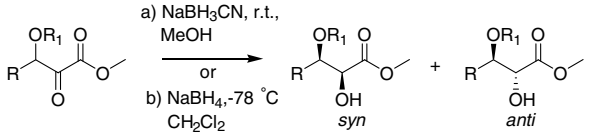
[a] Typically, a solution of the adduct in methanol or dichloromethane was treated with ozone at −78 °C for a few minutes (the solution should not become blue), after that, 10 equiv of dimethyl sulfide was added to the reaction medium at −78 °C, and finally, the reaction was left to achieve room temperature and stirred for about 16 h.
[b] The yields refers to isolated and purified products.
[c] All spectroscopic data are compatible with the proposed structures.
[d] Products proved to be unstable at room temperature, however, they are stable for a long time in a refrigerator.

occurs in many natural products, such as sugars, and also has an important role as ligand in asymmetric synthesis. Owing to their synthetic relevance, extensive efforts have been made to develop a general synthetic tool to stereoselectively produce 1,2-diols. Among the methods, we can cite the catalytic asymmetric dihydroxylation (AD) of olefins,[14] the stereoselective reduction of ketoesters,[15] hydroxylation of β-ketoesters[16] and aldol condensation.[17]

The importance of α,β-dihydroxy-esters in natural products chemistry and organic synthesis calls for the availability of as many as possible alternative methods to prepare these key compounds. As MBH adducts can be promptly prepared and as we demonstrated their easy transformation into α-ketoesters, our strategy seems to be an interesting alternative for the synthesis of α,β-dihydroxy-esters.

We started the reduction step using $NaBH_4$ in methanol at room temperature.[7] However, an extensive over-reduction was observed, which formed the corresponding triol in some cases. To circumvent this over reduction, we used a more selective hydride, sodium cyanoborohydride, which is indicated for the reduction of imines.[18] However, in the presence of a weakly acidic medium, this hydride can easily reduce carbonyl groups.[19] Initially we reduced the α-ketoesters prepared from the protected MBH adducts, but observed poor diastereoselectivity (Table 3, entries 1–3). Likely this result is due to the presence of the protecting group, which compromises the carbonyl face selection by the reducing agent. For all cases, *anti* isomers are the favored ones. Table 3 summarizes the results for the sodium cyanoborohydride reduction.[20]

Table 3. Reduction of the β-hydroxy-α-keto esters



R= aryl; R_1= TBS (**19**, **22**, **24**)
R= aryl; R_1= H (**27-31**)

R= aryl; R_1= TBS (**32-34**)
R= aryl; R_1= H (**35-39**)

Entry	R/α-ketoesters	(%)[a]	dr *syn*/*anti*[b]
1	**19**, R = phenyl; R_1 = TBS	**31** (70)	55:45[c]
2	**22**, R = 3,5-difluorophenyl, R_1 = TBS	**32** (86)	60:40[d]
3	**24**, R = 4-nitrophenyl, R_1 = TBS	**33** (93)	60:40[d]
4	**27**, R = phenyl, R_1 = H	**34** (70)[e]	5:95[c]
5	**28**, R = 4-OCH_3-phenyl, R_1 = H	**35** (61)	5:95[c]
6	**29**, R = 6-bromopiperonyl, R_1 = H	**36** (65)[e]	10:90[d]
7	**30**, R = 4-NO_2-phenyl, R_1 = H	**37** (70)	18:82[c]
8	**31**, 3-Cl-phenyl, R_1 = H	**38** (63)	5:95[d]

[a] Yields refer to purified and isolated compounds.
[b] Spectral data for all compounds are compatible with the proposed structures and relative stereochemistries (see, Ref. 11).
[c] Diastereoselectivity was determined by comparison with known compounds (after deprotection, if necessary—see Refs. 15b–f) or by NMR (of the corresponding acetals).
[d] The relative stereochemistry was ascertained by spectroscopic analysis of the corresponding acetals through NOE experiments.[21]
[e] Yield for two steps.

It is well-known that β-hydroxy ketone can be reduced with excellent diastereoselectivity when the hydroxyl group is free. Under this condition, the reduction takes place via a chelate intermediate normally with excellent diastereoselection.[15] We therefore reduced the α-ketoesters prepared from the direct ozonolysis of the unprotected MBH adducts. Owing to the relative instability of these compounds we decided to reduce them immediately after the evaporation of dimethyl sulfide. Fortunately, an excellent diastereoselectivity was obtained in all cases (Table 3, entries 4–8).

In summary, this study clearly demonstrates that the ozonolysis reaction of Morita–Baylis–Hillman adducts stemmed from aromatic aldehydes works efficiently thus providing access to valuable intermediates. This approach is therefore complementary to the elegant study conducted by Doutheau and co-workers.[8]

An asymmetric version of this approach could be easily developed simply by using chiral Morita–Baylis–Hillman adducts. Further studies aiming at to the application of this methodology for the synthesis of natural products and commercially valuable intermediates are ongoing in our laboratory. We also plan to study the use these aromatic ketoesters as intermediates for a reductive amination and for the preparation of tricarbonyl compounds.

Acknowledgements

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11. *Spectroscopic data of some representative examples of unprotected α-ketoesters*: (**28**) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.01 (s, 1H), 6.82 (s, 1H), 6.02 (s, 1H), 5.99 (s, 2H), 3.82 (s, 3H), 2.3 (br s, exchangeable with D_2O, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 192.7, 163.0, 148.3, 148, 121.3, 116.2, 113.2, 108.3, 101.2, 77.5, 52.5. HRMS (ESI) calcd for $C_{11}H_{10}BrO_6$ $[M+H]^+$ 316.9661; found 316.9652; (**30**) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55–7.20 (m, 4H aromatic), 5.82 (s, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.7, 162.9, 140.1, 134.1, 129.5, 128.2, 126.5, 124.5, 76.2, 52.6. HRMS (ESI) calcd for $C_{10}H_{10}ClO_4$ $[M+H]^+$ 229.0268; found 229.0233. *Spectroscopic data for some representative anti diols (unknown compounds)*: (**36**) ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.03 (s, 1H aromatic), 6.98 (s, 1H aromatic), 5.28 (d, $J = 3.9$ Hz, 1H), 4.54 (d, $J = 3.9$ Hz, 1H), 3.70 (s, 3H), 2.06 (br s, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 172.4, 147.9, 147.5, 131.4, 112.6, 112.4, 108.1, 101.8, 74, 73.4, 58.4. HRMS (EI, 70 eV) calcd for $C_{11}H_{11}BrO_6$ $[M]^+$ 317.9739; found 317.9723; (**38**) ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.35–7.15 (m. 4H aromatics), 4.99 (d, $J = 4.2$ Hz, 1H), 4.48 (d, $J = 4.2$ Hz, 1H), 3.71 (s, 3H), 2.77 (br s, 2H, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 172.1, 140.6, 134.3, 129.5, 128.3, 126.6, 124.5, 74.6, 74.4, 52.6. HRMS (ESI) calcd for $C_{10}H_{12}ClO_4$ $[M+H]^+$ 231.0424; found 231.0398.

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21. The relative stereochemistries of diols **24**, **35**, and **37** were determined by comparison with data available in the literature. The corresponding 1,2-ketals of diols **36** and **38** were used for stereochemical determinations.